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Review Article

CRITICAL CARE

Risk factors, biomarkers, and mechanisms for persistent inflammation, immunosuppression, and catabolism syndrome (PICS): a systematic review and meta-analysis

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Abstract

Introduction: Persistent inflammation, immunosuppression, and catabolism syndrome (PICS) has been proposed as an endotype of chronic critical illness (CCI). The aim of this systematic review is to synthesise the available evidence of risk factors, biomarkers, and biological mechanisms underlying PICS.

Methods: MEDLINE, CENTRAL, and EMBASE were searched on June 2, 2023. Our population of interest was adult intensive care unit survivors. The exposure group was patients with PICS and the comparator group was patients with no PICS, CCI, or rapid recovery. Mean differences were pooled for each biomarker using a random effects DerSimonian–Laird method. Risk of bias assessment was done using the Newcastle–Ottawa Scale.

Results: Six papers were included. Five were single-centre retrospective cohort studies, and one was a prospective cohort study, with sample sizes ranging from 22 to 391 patients. Two studies showed an increased incidence of PICS with age, and two studies showed an association between PICS and Charlson Comorbidity Index scores. PICS was associated with requiring mechanical ventilation in four studies. Meta-analysis showed a 34.4 mg L^{-1} higher C-reactive protein (95% confidence interval [CI] 12.7–56.2 mg L^{-1}; $P<0.01$), a 4.4 g L^{-1} lower albumin (95% CI 0.5–8.3 g L^{-1}; $P<0.01$), and a 0.36×10^9 L^{-1} lower lymphocyte count (95% CI 0.25–0.47×10^9 L^{-1}; $P=0.01$) in the PICS compared with the non-PICS group. There are a large variety of other potential biomarkers but limited validation studies. The overall quality of evidence is limited, and these results should be interpreted accordingly.

Conclusions: While older patients and those with co-morbidities could be at greater risk for PICS, acquired risk factors, such as injury severity, are potentially more predictive of PICS than intrinsic patient characteristics. There are many potential biomarkers for PICS, but limited validation studies have been conducted. Persistent myeloid-derived suppressor cell expansion, the continual release of danger-associated molecular patterns and pathogen-associated molecular patterns propagating inflammation, and bioenergetic failure are all mechanisms underlying PICS that could offer potential for novel biomarkers and therapeutic interventions.

Clinical trial registration: International Prospective Register of Systematic Reviews (PROSPERO; CRD42023427749).

Keywords: catabolism; chronic critical illness; immunosuppression; intensive care; persistent inflammation; PICS; post-intensive care syndrome

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Editor's key points

- Persistent inflammation, immunosuppression, and catabolism syndrome (PICS) has been proposed as an endotype of chronic critical illness (CCI).
- This systematic review and meta-analysis identified a large variety of potential biomarkers but limited validation studies, and the overall quality of evidence was limited.
- While older patients and those with co-morbidities could be at greater risk for PICS, acquired risk factors, such as injury severity, are potentially more predictive of PICS than intrinsic patient characteristics.
- Further studies are necessary to identify and validate potential biomarkers for PICS that will enhance diagnosis and therapeutic interventions.

About 7.6% of critically ill patients develop chronic critical illness (CCI),[1] defined as an intensive care unit (ICU) length of stay (LOS) of at least 14 days with evidence of persistent organ dysfunction,[2] and 30–50% of these patients show evidence of persistent inflammation, immunosuppression, and catabolism syndrome (PICS).[3] PICS consists of a self-perpetuating cycle of organ failure, inflammation, immunosuppression leading to recurrent infections, metabolic derangement, and muscle wasting.[4] The syndrome offers a mechanistic paradigm for this clinical phenotype that can be observed after a wide range of critical illnesses.[5,6] These patients commonly require long-term rehabilitation and frequent readmissions, and ultimately suffer an indolent death.[7]

There are many overlapping clinical and pathological features between CCI and PICS, although the causal relationship is unclear, with at least three possibilities.[8] Firstly, PICS represents a pathophysiological mechanism of CCI,[6] implying an onset before CCI. Secondly, PICS is a consequence of ongoing organ dysfunction in CCI,[7] implying PICS does not occur without CCI. Thirdly, PICS is an endotype of CCI,[9] implying other endotypes exist (Fig. 1). Understanding the pathophysiological basis of PICS is necessary to develop targeted treatment. Understanding risk factors and validation of diagnostic biomarkers will allow early identification and either prevention or prompt initiation of treatment.

The aim of this systematic review is to present the available evidence of potential risk factors, biomarkers, and biological mechanisms underlying PICS. We focus on PICS rather than the broader syndromes of CCI, persistent critical illness, or post-intensive care syndrome as PICS potentially offers a mechanistic paradigm and comprises a more defined group of patients who are likely to respond to similar targeted interventions.

Methods

This systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) *a priori* (CRD42023427749) on May 19, 2023. It is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) guidelines (Supplementary File 1).[10,11]

Search strategy

We used the following bibliographic databases: MEDLINE (via Ovid), CENTRAL, and EMBASE (via Ovid). The search was done on June 2, 2023 and the full search strategies for each database can be found in Supplementary File 2.

Inclusion and exclusion criteria

All relevant original research was included. There was no limit on publication dates. Unpublished studies, preprints, conference abstracts without subsequent study publication, studies not in English, review articles, editorials, and case reports were excluded. We excluded studies on paediatric patients (<16 yr old) and animal models. We used the original definition of PICS as ICU stay ≥10 days or prolonged hospitalisation >14 days, C-reactive protein (CRP) >1.5 mg L^{-1}, total lymphocyte count $<0.80\times10^{9}$ L^{-1}, and serum albumin <3.0 g dl^{-1}, creatinine height index <80%, weight loss >10%, BMI <18 kg m^{-2} during hospital admission, or retinol binding protein <10 μg dl^{-1}.[6] However, to ensure all potentially relevant studies were included, we opted for a lower CRP threshold of >0.5 mg L^{-1} as proposed.[9] The comparator/control group included patients with CCI, rapid recovery, or no evidence of PICS. The outcomes of interest were broad and included any possible risk factors, biomarkers, or biological factors for PICS. We anticipated this might have included, but not been limited to patient baseline characteristics, interventions received during ICU admission, vital signs, blood results, imaging, muscle biopsy results, and multi-omic data.

Selection and data extraction

Duplications were removed and two authors (KRC, EEB) independently screened all records (title and abstract) for inclusion/exclusion against the prespecified criteria above. Full text reports were retrieved for the included studies and the same two authors independently screened the texts, documenting reasons for any exclusions. Any disagreement was resolved through involvement of a third author (ZP). Data were extracted from the final included papers by one author (KRC) using Microsoft Excel™ (Microsoft Corp., Redmond, WA, USA) and checked by a second author (EEB). The extracted data included study details, patient characteristics, potential risk factors, blood results and biomarkers, and details on possible mechanisms of PICS, including biopsy or multi-omic data if present.

Data synthesis

Biomarkers reported in different units across the included studies were transformed to the most frequently reported unit for each biomarker (CRP mg L^{-1}, albumin g L^{-1}, lymphocyte count $\times10^{9}$ L^{-1}). In studies with a sample size >25, median values reported with inter-quartile ranges were converted to mean values and standard deviation using the Box–Cox method.[12] Mean differences were pooled for each biomarker using a random effects DerSimonian–Laird method. Between-study heterogeneity was evaluated using the I^2 test; we considered heterogeneity as I^2 >50%. Forest plots were generated for study-specific effect sizes along with 95% confidence intervals (CIs) and pooled effects. A P-value ≤0.05 was considered statistically significant. Meta-analysis of data was

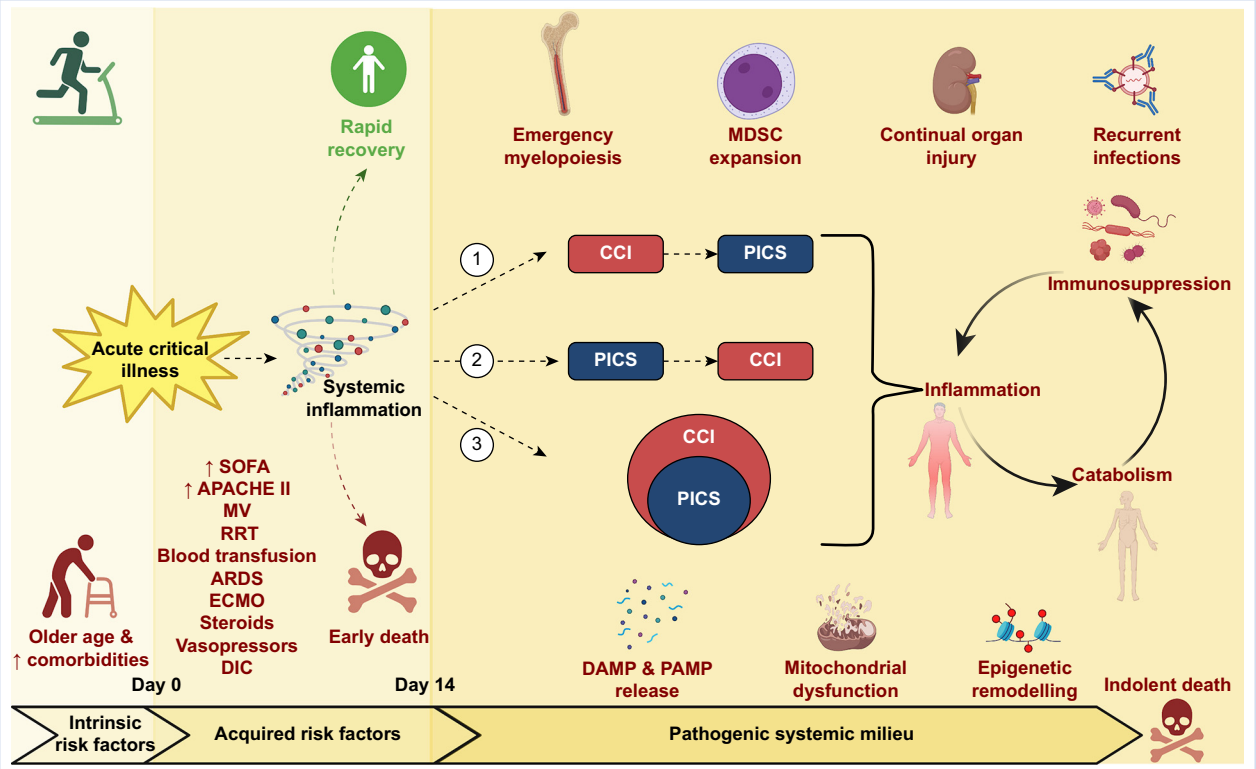

Fig 1. Summary diagram of the risk factors and pathophysiological mechanisms for PICS. An acute critical illness can lead to rapid recovery, early death, or CCI/PICS. Intrinsic risk factors before day 0 and acquired risk factors between days 0 and 14 for the development of CCI/PICS are shown. The three possible causal relationships between CCI and PICS are also shown. 1) PICS could be a consequence of ongoing organ dysfunction in CCI. 2) PICS could be a pathophysiological mechanism of CCI. 3) PICS could be an endotype of CCI. Finally, the diagram shows the pathogenic systemic milieux that have been linked to PICS and contribute to the self-perpetuating cycle of inflammation, immunosuppression, and catabolism, that can lead to indolent death. APACHE II, acute physiologic and chronic health evaluation; ARDS, acute respiratory distress syndrome; CCI, chronic critical illness; DAMP, danger-associated molecular pattern; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; MDSC, myeloid-derived suppressor cell; MV, mechanical ventilation; PAMP, pathogen-associated molecular pattern; PICS, persistent inflammation, immunosuppression, and catabolism syndrome; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment. Created with BioRender.com.

performed using the statistical software package Review Manager 5.4 (RevMan 5.4.1).

Quality and risk of bias assessment

Two authors (KRC, EEB) carried out a quality assessment using the GRADE tool and a risk of bias assessment using the Newcastle–Ottawa Scale for cohort studies.[13] The risk of bias as a result of missing results was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions. Any disagreement was resolved through discussion and consensus.

Results

Search results

We identified 7036 articles across three databases (Fig. 2). After removal of duplicates (n=2092), 4944 records were screened, of which 4350 were excluded as not relevant. The remaining 594 papers were compared with the inclusion and exclusion criteria, of which six papers met the inclusion criteria.[8,14–18]

The study details are summarised in Table 1. Five out of the six are single-centre retrospective cohort studies, and the remaining one is a prospective cohort study.[8] Four of the studies were based in China,[8,15,16,18] one in Japan,[17] and one in the Netherlands.[14]

The populations between studies differed, including trauma, surgical, emergency, and general medical patients. Two of the study populations had specific conditions of systemic lupus erythematosus (SLE)[16] and an enterocutaneous fistula (ECF).[15] The sample sizes ranged from 22 to 391 patients. The control groups differed and two studies had CCI patients as a control,[8,14] whereas the other four were based on patients without PICS, who might not have met criteria for CCI.[15–18] The prospective cohort study differed in that it compared four groups of patients: PICS only, PICS + CCI, CCI only, and no PICS or CCI.[8] There were differences in the PICS definition used but they all met the prespecified definition.[6,9] Hesselink and colleagues[14] provided a clinical and biomarker definition for PICS and we used results from their biomarker positive cohort as this matched our inclusion criteria.

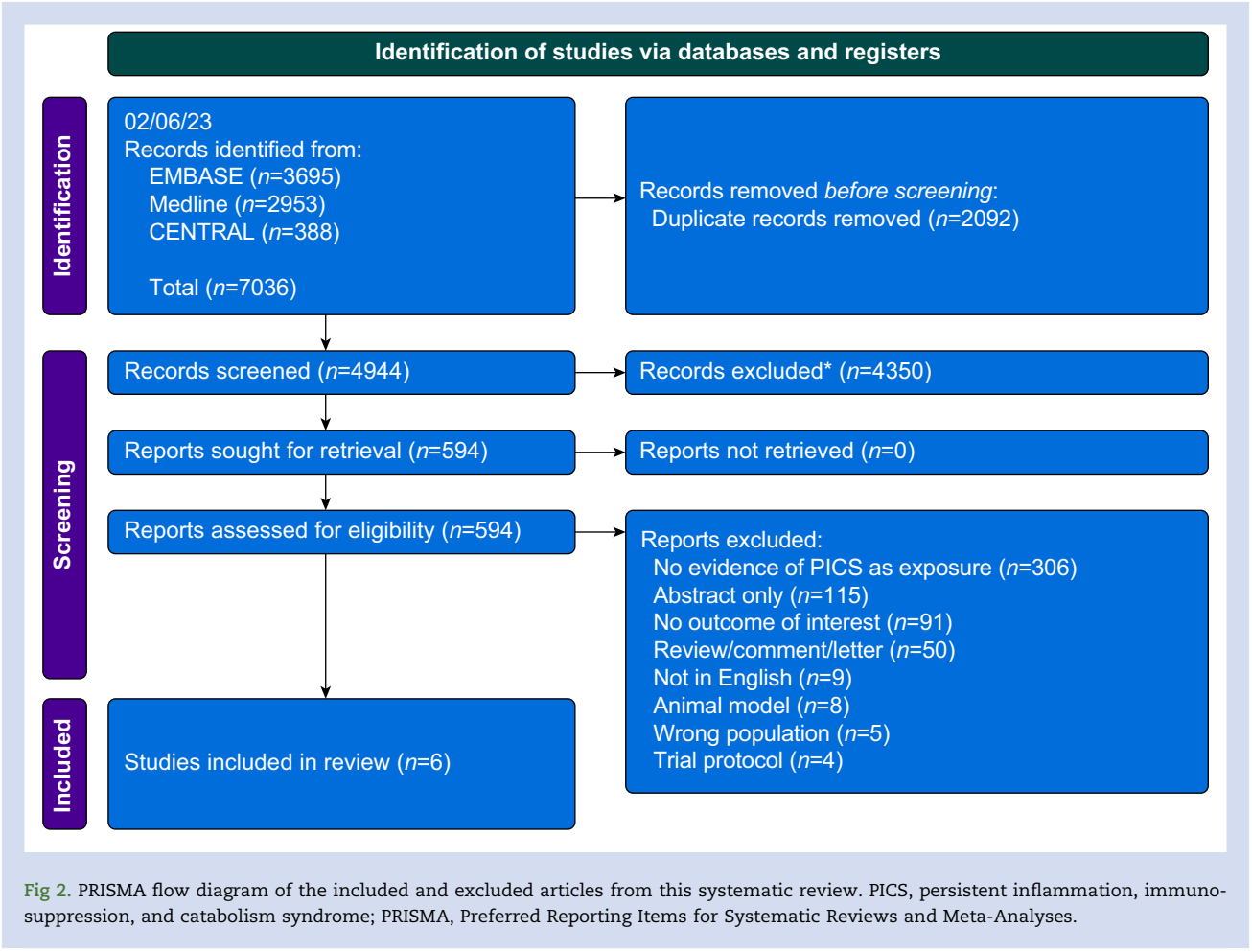

Fig 2. PRISMA flow diagram of the included and excluded articles from this systematic review. PICS, persistent inflammation, immunosuppression, and catabolism syndrome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Risk factors

Patient characteristics

All six studies reported age: two demonstrating associations with an increased incidence of PICS,[15,17] and four did not.[8,14,16,18] All six studies reported no association between sex and PICS.[8,14–18] Two out of six studies reported BMI results: one reporting a lower BMI as a risk factor for PICS (17.7 [0.21] *vs* 18.4 [0.15], $P<0.01$),[15] whereas the other did not (22.2 [19.5–26.2] *vs* 23.0 [20.2–25.0], $P=0.99$).[18] Five out of six studies reported APACHE II (acute physiologic and chronic health evaluation) scores. Two studies reported an association between APACHE II scores and PICS,[17,18] and two found no differences between groups.[8,16] Hu and colleagues[15] reported higher APACHE II scores in the PICS compared with the non-PICS group (11.3 [0.87] *vs* 8.14 [0.73], $P<0.01$) but gave different values for the non-PICS group in their table (9.20 [0.72]) with a non-significant *P*-value of 0.08.[15] Two out of six studies reported Charlson Comorbidity Index scores to be associated with PICS.[17,18] Two out of six studies reported SOFA (Sequential Organ Failure Assessment) scores to be associated with PICS.[8,18]

One study reported PICS to be associated with acute respiratory distress syndrome (ARDS) (34.3% *vs* 8.6%, $P<0.01$).[16] PICS is associated with use of steroids (13.9% *vs* 4.8%, $P<0.01$), immunosuppressants (1.3% *vs* 0.1%, $P=0.02$), vasopressors (53.2% *vs* 13.2%, $P<0.01$), extracorporeal membrane oxygenation (ECMO) (6.1% *vs* 0.4%, $P<0.01$), and shock on day 14 (39.4% *vs* 10.4%, $P<0.01$).[17]

Complications

Five out of six studies reported PICS to be associated with longer ICU LOS,[8,14–16,18] but not hospital LOS (three studies).[14,15,18] PICS was associated with a higher incidence of sepsis in three studies.[14,16,17] Another study showed no difference between PICS and non-PICS for early sepsis (75.5% *vs* 60.0%, $P=0.08$) but a higher incidence of late sepsis (after day 7 of admission).[15] One study reported a higher incidence of ICU acquired infection with PICS,[18] whereas another found no differences in secondary infections between groups.[8] Two studies showed that PICS was associated with pneumonia,[14,15] one with catheter-related bloodstream infections,[15] and one showed no difference between infection sites.[16]

PICS was associated with requiring mechanical ventilation in four studies.[14–17] Three out of six studies reported conflicting incidences of renal replacement therapy (RRT): two studies demonstrated an association,[14,17] whereas one study on patients with SLE did not.[16] Similar conflicting relationships are seen with reported surgical procedures in two

Table 1 A summary of the main study details for the included papers. CCI, chronic critical illness; CKD, chronic kidney disease; ECF, enterocutaneous fistula; ICU, intensive care unit; PICS, persistent inflammation, immunosuppression, and catabolism syndrome; SLE, systemic lupus erythematosus.

Reference	Year	Setting	Study type	Aims	Population	Exposure	Exposure *n*	Control	Control *n*	Inclusion criteria	Exclusion criteria
Hesselink and colleagues[14]	2020	University Medical Center Utrecht, Netherlands	Single-centre retrospective cohort	Investigate incidence of PICS after trauma, determine the clinical course, and test postulated markers to identify PICS patients	Trauma patients ≥14 days in ICU	Clinical PICS or PICS markers positive	22	CCI with no PICS	78	1. ≥16 yr old 2. ICU stay ≥14 days	1. ICU admission for other reasons than critical illness 2. Isolated neurotrauma
Hu and colleagues[15]	2014	Jinling Hospital, Nanjing University, China	Single-centre retrospective cohort	Examine the prevalence and characteristics of PICS and its impact on the outcome of ECF patients	Patients with ECF admitted to ICU	ECF+PICS	53	ECF+no PICS	70	1. Patients with ECF admitted to ICU	1. Terminal malignant tumour 2. Transferred to another hospital
Li and colleagues[16]	2023	Jinling Hospital, Nanjing University, China	Single-centre retrospective cohort	Analyse the clinical characteristics and prognosis of SLE complicated with PICS, and the risk factors affecting prognosis	SLE patients on ICU >14 days	SLE+PICS	61	SLE+no PICS	35	1. SLE 2. ICU LOS >14 days	1. Age <18 or >70 yr 2. Regular dialysis started in CKD5 3. Loss to follow-up
Suzuki and colleagues[17]	2022	Toho University Omori Medical Center, Japan	Single-centre retrospective cohort	Investigate the relationship between blood transfusions and PICS	ICU patients who survived 14 days or more of admission	PICS	391	No PICS	762	1. Tertiary emergency patients admitted to the ICU	1. Age <18 yr 2. Death within 14 days of admission to the ICU. 3. Acute deterioration in hospital 4. Scheduled to undergo surgery
Zhong and colleagues[18]	2021	Ruijin Hospital, China	Single-centre retrospective cohort	Find the predictors for PICS in ICU surgical septic patients	Surgical ICU patients	PICS	47	No PICS	122	1. ≥18 yr old 2. Admitted to ICU after major surgery or within 48 h after the diagnosis of sepsis	1. Pregnant or lactating patients 2. Severe immune deficiency 3. Death within 14 days of sepsis diagnosis

Continued

Table 1 Continued

Reference	Year	Setting	Study type	Aims	Population	Exposure	Exposure n	Control	Control n	Inclusion criteria	Exclusion criteria
Zhou and colleagues[8]	2023	Suzhou Municipal Hospital and Suzhou Ninth People's Hospital, China	Prospective cohort	Investigate and compare the clinical features and prognosis of CCI/PICS	ICU patients with LOS ≥14 days	PICS, CCI+PICS	17 50	CCI only, No CCI or PICS	71, 30	1. ≥18 yr old 2. ICU LOS ≥14 days	1. ICU LOS <14 days 2. Long-term use of immunosuppressants, corticosteroids, or both 3. Congenital immunodeficiency, acquired immunodeficiency, or both 4. Pregnancy 5. No consent

studies, one demonstrating a higher association[17] and one not.[14] Infusion of blood products, specifically red blood cells, plasma, and platelets, was shown to be associated with PICS.[17] No association between PICS and instigation of a massive transfusion protocol was seen in another study.[14]

Blood results and biomarkers

Pooled analysis

Meta-analysis of pooled studies showed a 34.4 mg L^{-1} higher CRP (n=2863; 95% CI 12.7–56.2 mg L^{-1}; P<0.01), a 4.4 g L^{-1} lower albumin (n=2863, 95% CI 0.5–8.3 g L^{-1}; P<0.01), and a 0.36×10^9 L^{-1} lower lymphocyte count (n=2810; 95% CI 0.25–0.47 ×10^9 L^{-1}; P=0.01) in the PICS compared with the non-PICS group (Fig. 3).

Individual studies

One study differentiated patients who met PICS criteria by biomarkers, and those with clinical evidence. Out of the 22 patients in the PICS marker positive group, eight had clinical evidence of PICS, giving a sensitivity and specificity of these PICS markers (lymphocytes, CRP, and albumin) as 44% and 77%, respectively.[14] No difference in lymphocyte or CRP levels was seen between groups.[14] Two studies showed no difference in CRP levels between groups,[15,18] in contrast to two other studies showing a higher CRP with PICS.[16,17] One other study reported higher CRP levels in the PICS and CCI group (67.7 mg L^{-1} [32.9–138.8 mg L^{-1}]) compared with the PICS only group (14.1 mg L^{-1} [5.6–78.4 mg L^{-1}]) and the non-PICS and non-CCI group (21.4 mg L^{-1} [9.7–59.1 mg L^{-1}]) on day 21 but no differences on days 1 and 14.[8]

Reduced total lymphocyte counts and levels of CD3, CD4, CD8, and CD20 were associated with PICS.[16] PICS was associated with lower total lymphocyte counts on admission, day 3, day 14, and day 21.[8,17,18] In a univariate logistic regression analysis, there were differences between PICS and non-PICS in CRP on day 14, lymphocyte and albumin levels on days 1 and 14, and neutrophil, albumin, and CRP levels on day 21, but in multivariate analyses, lymphocyte levels were not significant.[8] The only included study to report the neutrophil:lymphocyte ratio (NLR) found it was higher on day 3 in PICS compared with non-PICS (16.9 [10.3–26.4] *vs* 10.5 [7.2–17.9], p<0.01) but not on day 1.[18] Li and colleagues[16] reported no difference in albumin between groups.[16] No difference in albumin between groups was seen on day 1[8] or day 3.[18] However, four other studies showed an association between PICS and low albumin levels,[15] on admission,[17,18] and days 14 and 21.[8]

PICS was associated with raised inflammatory markers, namely procalcitonin (2.19 μg L^{-1} [0.58–9.18 μg L^{-1}] *vs* 0.68 μg L^{-1} [0.26–1.97 μg L^{-1}], P<0.01) and interleukin-6 (IL-6) (224 ng L^{-1} [64.2–618 ng L^{-1}] *vs* 39.1 ng L^{-1} [22.7–84.6 ng L^{-1}], P<0.01).[16] Lower haemoglobin level and platelet count were associated with PICS, and lower urea and creatinine.[16] Another study similarly showed a reduced haemoglobin level with PICS, but higher creatinine levels.[17] The same study showed further associations of PICS with higher lactate levels and disseminated intravascular coagulation.[17]

Risk of bias assessment

Using the Newcastle–Ottawa Scale, three studies were at moderate risk of bias[14–16] and three studies as low risk[8,17,18] (Supplementary File 3). Using the GRADE assessment tool,

the included studies were deemed very low quality for the outcomes of risk factors and biomarkers for PICS (Supplementary File 4). Our pooled analysis of lymphocyte count is missing data from Hu and colleagues[15] because of unavailable results. The missing data are unlikely to be because of the magnitude or direction of the results because lymphocyte count was not used as a specific outcome in the study, however selective non-reporting of results cannot be ruled out indicating a high risk of bias. Funnel plots were not used because of the low number of studies.

Discussion

Persistent inflammation, immunosuppression, and catabolism syndrome is seen after a wide range of critical illnesses and accounts for significant morbidity and mortality.[5,6] As its components are potentially reversible, it is a classification system that potentially offers mechanistic insight for targeted intervention. However, the definitions for PICS vary in the literature.[19] Despite PICS being first described >10 yr ago, this systematic review has highlighted the lack of studies comparing this specific cohort of patients with early death, rapid recovery, or CCI cohorts. Furthermore, there are no randomised controlled trials targeting patients with PICS specifically.

Risk factors

The included studies show conflicting results for intrinsic risk factors for PICS, such as age. Other studies have shown that older patients are more likely to develop CCI.[20–22] Furthermore, older patients had more persistent abnormalities in PICS biomarkers 14 days post-sepsis.[23] The acquired risk factors, such as type and severity of injury, are potentially more important in predicting PICS, suggesting that PICS is more than a manifestation of frailty and previous co-morbidities. This is supported by an analysis on 102 patients with haemorrhagic shock using k-means clustering, which identified a hyperinflammatory endotype associated with the highest incidence of CCI, infections, and LOS, and two rapid recovery endotypes. There were no differences in baseline characteristics, such as age, sex, co-morbidities, and BMI, between the three endotypes but the hyperinflammatory endotype was associated with a higher injury severity and blood transfusion requirements.[24] This is supported by some of the included studies showing PICS is associated with higher APACHE II scores,[17,18] SOFA scores,[8,18] ARDS,[16] mechanical ventilation,[14–17] RRT,[14,17] blood transfusions,[17] ECMO,[17] and use of steroids, immunosuppressants, and vasopressors[17] (Fig. 1). Reliable biomarkers could be a more objective way of accurately predicting risk and making early diagnosis.

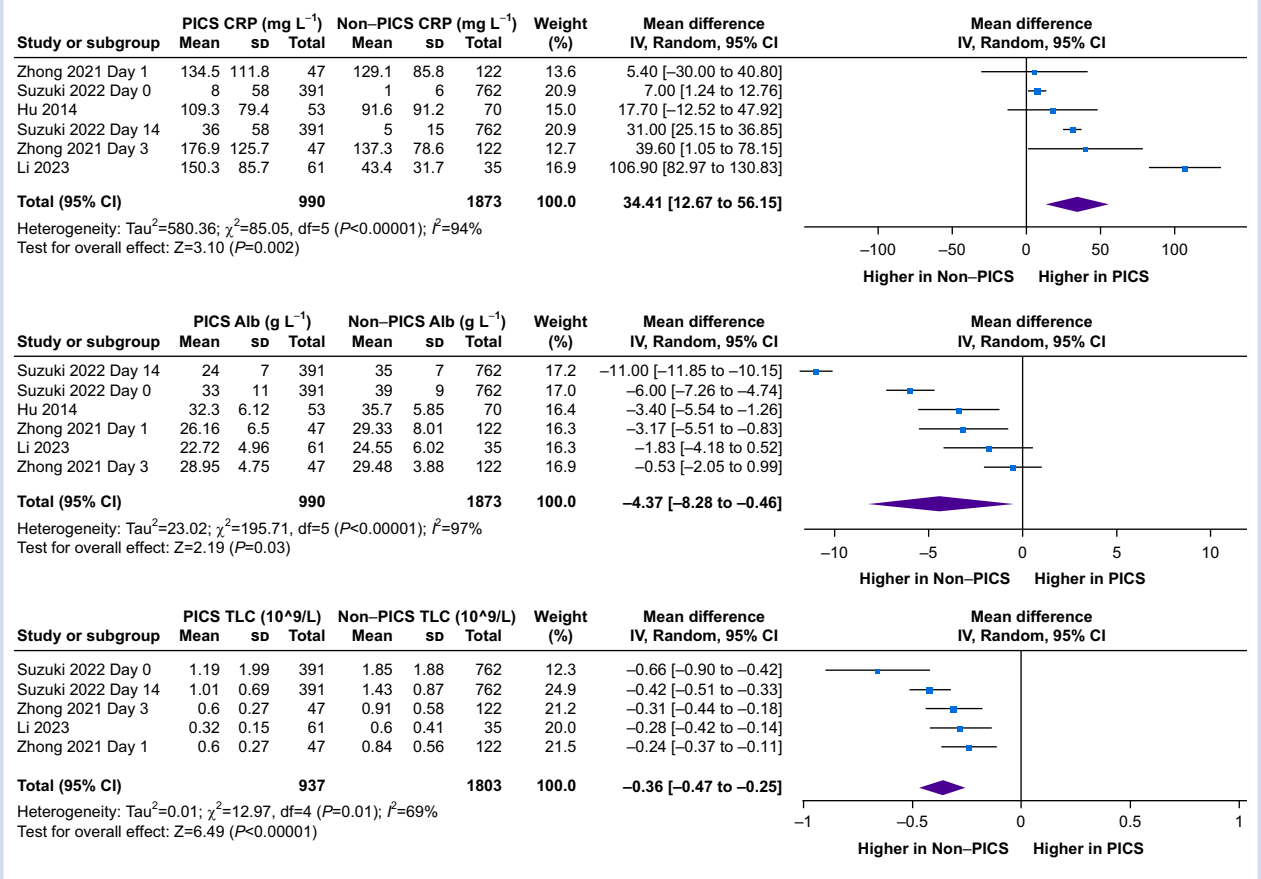

Fig 3. Forest plots of studies reporting biomarker outcomes demonstrated as a weighted mean difference using frequentist meta-analysis. Alb, albumin; CI, confidence interval; CRP, C-reactive protein; df, degrees of freedom; PICS, persistent inflammation, immunosuppression, and catabolism syndrome; SD, standard deviation; TLC, total lymphocyte count.

Blood tests and biomarkers

C-reactive protein, lymphocyte, and albumin levels are part of the diagnostic criteria for PICS. Our meta-analysis confirmed the expected differences in these biomarkers between PICS and non-PICS, albeit with high levels of heterogeneity. Conflicting results among the individual studies might be as a result of differences in the timing of biomarker measurement, which requires standardisation, or because of the nonspecific nature of these biomarkers.[14] Trajectories, as opposed to single absolute values, might be helpful in diagnosing PICS. Group-based trajectory modelling noted a persistent lymphopaenia endotype to have the highest incidence of PICS.[25]

There is a growing interest in studying other biomarkers for PICS (Fig. 4). CCI patients have higher biomarker levels of inflammation (IL-6, IL-8, interferon gamma-induced protein [IP-10], monocyte chemoattractant protein 1), immunosuppression (IL-10, soluble programmed death ligand-1), stress metabolism (glucagon-like peptide 1 [GLP-1]), catabolism markers (plasma insulin-like growth factor binding protein 3 and urinary 3-methylhistidine excretion) and angiogenesis (angiopoietin-2, vascular endothelial growth factor [VEGF], VEGF receptor-1, stromal cell-derived factor).[26,27] Both the NLR and monocyte:lymphocyte ratio reflect immune activation and inflammation in critical illness and correlate with clinical severity.[28–30]

Most, but not all, included studies showed PICS is associated with low albumin levels. Other more specific biomarkers of catabolism have been studied. For example, elevation of GLP-1 at 24 h is an independent predictor for development of CCI. GLP-1 remains high at day 21 in sepsis survivors with CCI, suggesting it might be a biomarker for the non-resolving catabolic state that occurs in PICS.[31] An elevated urea:creatinine ratio (UCR) occurs with muscle wasting and provides a biochemical signature for PICS.[32] The UCR was significantly increased in persistent critical illness (PerCI) compared with the control group.[33] The UCR also performed better at discriminating catabolism than albumin levels.[34]

Anaemia and coagulopathy have both been implicated in CCI and PICS in animal and human studies.[35–37] Further research is needed to establish the role that coagulopathy and microthrombi formation could play in the clinical trajectory of PICS. None of the included studies looked at lipid levels as potential biomarkers for PICS, but several studies have for CCI. One such study revealed a hypolipoprotein cluster, characterised by lower lipoprotein levels, higher SOFA scores, increased endothelial dysfunction (intercellular adhesion molecule-1 [ICAM-1]), and a higher incidence of CCI.[38] Another study demonstrated an early loss of circulating lipids followed by a delayed and selective increase in predominately diacylglycerols (DAG), triglycerides (TAG), and phosphatidylethanolamines (PE) in patients with PerCI.[39] The decline in circulating lipids could reflect the uptake and catabolism of lipids to meet the energy requirements of critical illness. The increase of DAG, TAG, and PE could reflect enhanced lipogenesis and ongoing systemic inflammation and metabolic stress.[39] Lipid levels or other metabolic markers could therefore be potential biomarkers in PICS.

Pathophysiology

There is a limited number of biomarker studies on patients with PICS. Developing our understanding of the pathophysiology of PICS will help inform future work on potential novel, disease-specific biomarkers relating to immunosuppression, inflammation, or catabolism.

Immunosuppression

Emergency myelopoiesis in response to tissue injury results in rapid release of mature myeloid populations leading to store depletion and release of immature populations.[40] In a murine model, 7 days post-sepsis, 90% of the bone marrow were myeloid cells, mostly immature and functionally immunosuppressive.[41] The increased myeloid cell production is favoured at the expense of lymphopoiesis and erythropoiesis, leading to immunosuppression and anaemia, respectively.[42] Emergency myelopoiesis leads to expansion of a heterogenous group of inducible immature myeloid cells, named myeloid-derived suppressor cells (MDSCs).[43–45] MDSCs have a role in protecting host innate immunity[46] and mediating inflammation through production of reactive oxygen species (ROS), nitric oxide, tumour necrosis factor α, regulated on activation, normal T-cell expressed and secreted (RANTES), and macrophage inflammatory protein 1β (MIP-1β).[41,47] MDSCs have been shown to become more immunosuppressive with time.[42,48]

After sepsis, MDSCs remain elevated for 6 weeks, and suppress T-cell proliferation and IL-2 production after 2 weeks.[49] Circulating MDSCs post-sepsis are associated with longer ICU LOS, secondary infections, and poor functional outcomes.[42,50,51] MDSC expansion persisted for 28 days in septic patients, with inhibited T cell proliferation *in vitro* and reduced T_{H1} and T_{H2} cytokine release.[42] Emergency myelopoiesis is impaired in the older population.[3] Aged mice have a higher mortality from secondary infection after failure of bone marrow progenitors to initiate and complete an emergency myelopoietic response, rather than from an exaggerated inflammatory insult.[52] Older patients are also less able to resolve their initial inflammatory response.[52] Unresolved inflammation leads to continued pathological expansion and activation of MDSCs, which further trigger inflammation and immunosuppression.[5]

Inflammation

Elevation of inflammatory markers can persist for at least 28 days after sepsis.[53] Alarmins are likely to mediate persistent inflammation in PICS. Pattern-recognition receptors (PRRs) bind to alarmins from two sources.[5] Exogenous pathogen-associated molecular patterns (PAMPs) arise from reactivation of latent viral infections or nosocomial infections. PAMPs trigger dendritic cell maturation for antigen processing, MHC expression, and migration to lymph nodes to stimulate T cells.[54] Secondly, endogenous alarmins from damaged cells release danger-associated molecular patterns (DAMPs),[55] such as nuclear DNA, high mobility group box 1 (HMGB1), and S100, which are raised in septic patients throughout their admission[56–58] and contribute to persisting low-grade inflammation in PICS.[9] The inflammation results in oxidative stress and subsequent mitochondrial dysfunction and bioenergetic failure that further aggravates the inflammatory pathways. This leads to a self-perpetuating cycle of inflammation and organ injury.[5,59]

Catabolism

Patients with CCI and PICS experience prolonged muscle wasting and cachexia, resulting from a disruption of the balance between muscle protein synthesis and breakdown.[5] Muscle loss can reach up to 2–3% per day and is most rapid in the acute phase, but, in prolonged critical illness this catabolic state continues for up to 30 days.[60–62] Muscle biopsies in

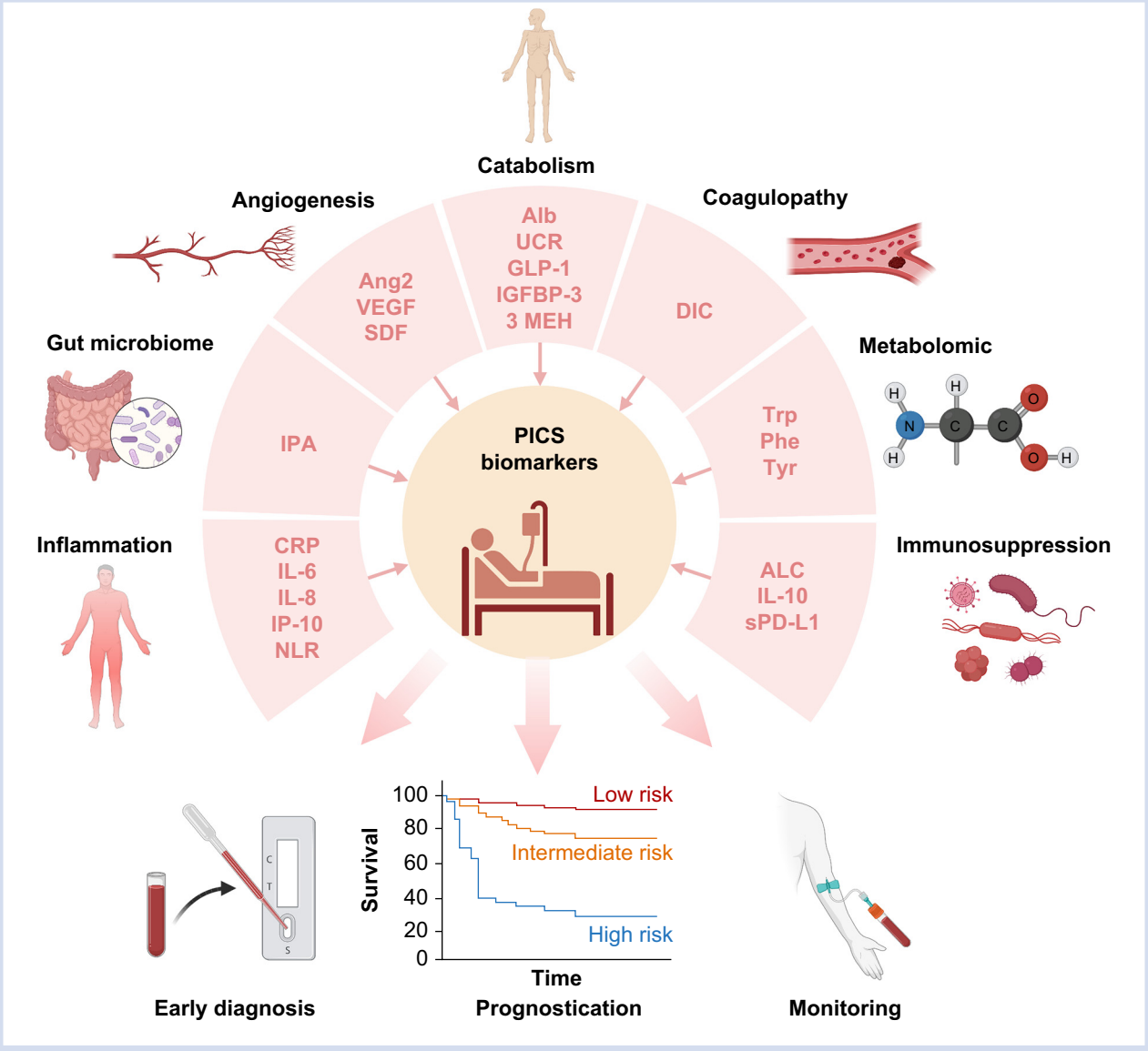

Fig 4. Summary diagram of potential biomarkers for PICS. This illustration highlights a range of biomarkers, organised by pathophysiological mechanism, and their potential utility in the early diagnosis, prognostication, and monitoring of PICS. 3 MEH, urinary 3-methylhistidine; Alb, albumin; ALC, absolute lymphocyte count; Ang2, angiopoietin-2; CRP, C-reactive protein; DIC, disseminated intravascular coagulation; GLP-1, glucagon-like peptide-1; IGFBP-3, insulin-like growth factor binding protein 3; IL-6, interleukin 6; IL-8, interleukin 8; IL-10, interleukin 10; IP-10, interferon gamma-induced protein; IPA, indole-3-propionate; NLR, neutrophil:lymphocyte ratio; Phe, phenylalanine; PICS, persistent inflammation, immunosuppression, and catabolism syndrome; SDF, stromal cell-derived factor; sPD-L1, soluble programmed death ligand-1; Trp, tryptophan; Tyr, tyrosine; UCR, urea: creatinine ratio; VEGF, vascular endothelial growth factor. Created with BioRender.com.

critically ill patients show intramuscular inflammation and myocyte necrosis with both neutrophil and macrophage infiltration.[61] Systemic inflammation acts as an anti-anabolic signal, decreasing muscle protein synthesis, and increasing insulin resistance, leading to impaired glucose utilisation and muscle atrophy.[62] Mitochondrial dysfunction reduced mitochondrial numbers and density, and mitochondrial swelling has been reported in critical illness.[63,64] The resultant bioenergetic crisis leads to myocyte necrosis and the intramuscular inflammation observed in biopsies.[62] This is supported by a study on ventilated patients with ICU-acquired weakness showing ~50% reduction of aerobic ATP synthesis in skeletal muscle compared with controls, linked to depletion of mitochondrial complexes III and IV.[64]

Practical implications

Given our ageing population and the increased provision of critical care services, patients with PICS are a growing cohort. This review has several practical implications. For academics, the low number of included studies has highlighted the need for a standardised population and definitions in order to

conduct further clinical studies. For clinicians, it has summarised our current understanding of risk factors and biomarkers of PICS that have potential to better risk stratify patients, prognosticate, and diagnose patients at earlier stages. Furthermore, the pathophysiological summary of PICS demonstrates the potential therapeutic targets for intervention. For policymakers, the absolute pooled values can be used in future work to help define precise, evidence-based cut-off values for PICS that will standardise data collection. This can aid with assessing the prevalence and incidence of the condition and allocating appropriate resources to help survivors of critical illness with PICS to recover.

Limitations

There are only a small number of low-quality studies comparing patients with PICS against CCI or rapid recovery patients. The risk of bias in the included studies was low to moderate and there was a possibility of selective non-reporting of data limiting the ability to draw conclusions from our evidence synthesis. Furthermore, the six included studies used varying definitions of PICS and two of the studies were on specific cohorts of patients. Meta-analysis of biomarkers was performed but required transformation of data possibly introducing uncertainty in the data. Four of the studies were in China, which could limit the external validity of the results when considering other healthcare settings. Five of the studies were single centre, adding to this issue. All the studies were observational, limiting the ability to make any casual inferences from the data. Another challenge is the lack of pre-admission data on this cohort of patients, as it is difficult to establish whether PICS is induced by the critical illness insult or a manifestation of frailty and other co-morbidities. Future research could consider studying surgical patients admitted to ICU as these patients will likely have the relevant preadmission data for comparison as part of their perioperative assessment. The limited available studies on PICS means that the results of this systematic review should be interpreted with appropriate circumspection.

Conclusions

Although older patients and those with co-morbidities may be at greater risk for persistent inflammation, immunosuppression, and catabolism syndrome (PICS), acquired risk factors, such as injury severity, are potentially more predictive of PICS than intrinsic patient characteristics. There are many potential biomarkers for PICS, but limited validation studies have been conducted. Persistent myeloid-derived suppressor cell expansion, the continual release of danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) propagating inflammation, and bioenergetic failure are all significant mechanisms underlying PICS that could offer potential for novel biomarkers and therapeutic interventions.

Authors' contributions

Conception: KRC, ZP
Supervision: ZP
Data extraction: KRC, EEB
Data analysis and interpretation: all authors
Drafting the original manuscript: KRC
Revising subsequent drafts: all authors
Approved the final version of the article to be published: all authors

Declaration of interest

ZP has received honoraria for consultancy from Nestlé, Nutricia, Faraday Pharmaceuticals, and Fresenius-Kabi and speaker fees from Baxter, Fresenius-Kabi, Nutricia, and Nestlé. The other authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2024.03.038.

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